UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/567,872	05/19/2006	Ilia Fishbein	RCHP-135US	1203

23122 7590 12/10/2008
RATNERPRESTIA
P.O. BOX 980
VALLEY FORGE, PA 19482

EXAMINER	
SHEN, WU CHENG WINSTON	
ART UNIT	PAPER NUMBER
1632	
MAIL DATE	DELIVERY MODE
12/10/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/567,872	FISHBEIN ET AL.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 8-38* is/are pending in the application.

4a) Of the above claim(s) *2,4-6 and 11-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,8-10 and 33-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 February 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08/20/2008, 09/03/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim amendments filed on 08/20/2008 have been received and entered. Claim 7 is cancelled. Claims 33-38 are newly added. Claims 1-6, and 8-38 are pending. Claims 1, 3, 8-10, and 33-38 are currently under examination.

Claims 2, 4-6, and 11-32 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim.

This application 10/567,872 is a 371 of PCT/US04/26509 filed on 08/13/2004, which claims benefit of 60/494,886 filed on 08/13/2003.

Claim Rejection - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

1. Claim 33 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. *This rejection is necessitated by claim amendment filed by Applicant on 08/20/2208 adding claim 33.*

Newly added claim 33 recites "wherein the modified protein comprises at least one of a fusion protein and a polypeptide". It is unclear the relationship between "a polypeptide" and "a fusion protein" in this wherein clause. The limitation "at least a fusion protein" is clear. The

limitation "at least a fusion polypeptide" is clear. However, "at least one of a fusion protein and a polypeptide" is unclear.

Claim Rejection - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

2. Previous rejection of claims 1 and 3 under 35 U.S.C. 102(a) as being anticipated by Sharma et al. (Sharma et al., Study of protein splicing and intein-mediated peptide bond cleavage under high-cell-density conditions. *Biotechnol Prog.* 19(3): 1085-90, 2003; this reference is cited on pages 5 of Restriction requirement dated 11/08/2007), is ***withdrawn*** because the claims have been amended.

Claim 1 has been amended to read as follows: A composition comprising a metal surface and a modified protein, wherein the modified protein is covalently bound to the metal surface.

Claim 3 has been amended to read as follows: The composition of claim 1, wherein the modified protein is covalently bound to the metal surface through a thiol residue and a linker.

Sharma et al. does not teach the amended limitation "metal surface".

3. Claims 1, 3, 8, and 10 remain rejected and newly added claims 33 and 38 are rejected under 35 U.S.C. 102(b) as being anticipated by Halbreich et al. (U.S. patent No. 6,150,181, issued Nov. 21, 2000). Applicant's arguments filed 08/20/2008 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 4-6 of the office action mailed on 05/22/2008.

For clarity and completeness of this office action, the rejection for the reasons of record advanced on pages 3-4 of the office action mailed on 05/22/2008, is revised below to address claim amendments filed on 08/20/2008.

Amended claim 1 is drawn to a composition comprising a metal surface and a modified protein covalently bound to the metal surface. Claim 3 limits the modified protein being covalently bound to the metal surface through a thiol residue (i.e. -SH functional group) and a linker. Claim 8 limits the metal surface being a surface of a medical device. Claim 10 further limits claim 8 to the medical device being at least one of an internal device and an external device. Newly added Claim 33 limits the modified protein comprises at least one of fusion protein and a polypeptide. Claim 38 limits the medical device is coated with a layer of linker and a layer of the modified protein.

Halbreich et al. teaches magnetic nano-particles (mean diameter 9 nm) named ferrofluid (FF), which is made of the ferrites MFe_2O_4 (including magnetite Fe_3O_4) and maghemite γ Fe_2O_3 (which is encompassed by the limitation, metal surface, recited in amended claims 1 and 3 of instant application), and the surface of the magnetic nano-particles are coated/coupled with an effector protein, including recombinant protein annexine (Anx) V and an antibody of interest

(which reads on the limitation on the modified protein comprises at least one of fusion protein and a polypeptide recited in claim 33). The coupling between magnetic nano-particles and effector protein of interest is achieved by the use of difunctional compounds (i.e. cross linkers) such as N-succinimdyl 3-(2-pyridyldithio) propionate (SPDP), which make it possible to bond an effector protein to the particles via a peptide bond and a disulfide bridge (S-S) (which is encompassed by the limitation, a thiol residue and a linker, recited in claim 3 of instant application, and the limitations of newly added claim 38), without damage to the protein (See lines 38-40, column 1, and lines 2-7, 33-50, column 2, Halbreich et al., 2000), which is encompassed by the limitation modified protein recited in claim 1 of instant application.

Claim 8 is rejected because Halbreich et al. teaches using Anx FF (i.e. annexine covalently linked to ferrofluid nano-particles) as a medical device to analyze the retention of erythrocytes (i.e. formation of erythrocyte-Anx FF complex) in the blood samples of patients (See Figure 5, and Table 1 in column 10, Halbreich et al., 2000).

Claim 10 is rejected because the magnetic nano-particles Anx FF used for analysis of the retention of erythrocytes in the blood samples of patients, taught by Halbreich et al., are considered as an external medical device (when blood is taken out of a patient) and/or an internal medical device (when blood remains in a patient).

Thus, Halbreich et al. clearly anticipate claims 1, 3, 8, 10, 33, and 38 of instant application.

Applicant's arguments

Applicant states that claims claim 1, and claims 3, 8, and 10 which depend from claim 1, have been amended to specify that the surface is a "metal" surface. Applicant argues that

maghemite is an iron oxide, and nanoparticles comprising maghemite taught by Halbreich et al. do not provide a metal surface.

Response to Applicant's arguments

The amended claims do not specify the composition of recited "metal surface" and the specification does not define what "metal surface" is, nor does the specification indicate what kind of metal(s) is/are present in the claimed metal surface. The reasonable interpretation of recited "metal surface" certainly reads on magnetic nano-particles named ferrofluid (FF), which is made of the ferrites MFe_2O_4 (including magnetite Fe_3O_4) and maghemite γ Fe_2O_3, taught by Halbreich et al. It is further noted that Halbreich et al. teaches that the coupling between magnetic nano-particles and effector protein of interest is achieved by the use of difunctional compounds (i.e. cross linkers) such as N-succinimdyl 3-(2-pyridyldithio) propionate (SPDP), which make it possible to bond an effector protein to the particles via a peptide bond and a disulfide bridge (S-S). The same cross linkers SPDP is used by the instant application (See Figure 1, 2007/0092489, publication of instant application). As the coupling processes of the methods taught by Halbreich et al. and by instant application involve same crossing linking agent and formation of covalent S-S bridges, the magnetic nano-particles made of the ferrites MFe_2O_4 (including magnetite Fe_3O_4) and maghemite γ Fe_2O_3 taught by Halbreich et al. clearly anticipate the metal surface claimed by instant application.

4. Claims 1 and 8-10 remain rejected and newly added claims 33 and 38 are rejected under 35 U.S.C. 102(b) as being anticipated by Feijen et al. (U.S. patent No. 4,634,762, issued Jan. 6, 1987). Applicant's arguments filed 08/20/2008 have been fully considered and they are not

persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on page 6 of the office action mailed on 05/22/2008.

For clarity and completeness of this office action, the rejection for the reasons of record advanced on page 6 of the office action mailed on 05/22/2008, is revised below to address claim amendments filed on 08/20/2008.

Amended claim 1 is drawn to a composition comprising a metal surface and a modified protein covalently bound to the metal surface. Claim 8 further limits the metal surface being a surface of a medical device. Claim 9 further limits claim 8 to medical device selected from the group consisting of a stent, a heart valve, a wire suture, a joint replacement, a urinary dilator, an orthopedic dilator, a catheter, and an endotracheal tube. Claim 10 further limits claim 8 to the medical device being at least one of an internal device and an external device. Newly added Claim 33 limits the modified protein comprises at least one of fusion protein and a polypeptide. Claim 38 limits the medical device is coated with a layer of linker and a layer of the modified protein.

Feijen et al. teaches conjugates for coating a surface of a medical device and the conjugates are covalently bonded conjugates of an anticoagulant and protein that are prepared in the presence of a coupling agent that forms amide linkages between the anticoagulant and the protein (which reads on the limitations recited in claims 1, 8-10, 33, and 38 of instant application) (See abstract, Feijen et al., 1987). Feijen et al. teaches these conjugates are useful for enhancing the blood compatibility of certain surfaces of a prosthetic device (which is encompassed by internal device recited in claims 1 and 10 of instant application), a surgical apparatus (which inherently reads on the metal surface of a medical device recited in claim 8),

or an extra-corporeal medical device (which is encompassed by external device recited in claims 1 and 10 of instant application) (See abstract, Example 2, claim 18, Feijen et al. 1987). Feijen et al. teaches extra-corporeal medical device includes a catheter (which is encompassed by claims 1, 8-9 of instant application) (See lines 24-38, column 4, Feijen et al.)

Thus, Feijen et al. clearly anticipate claims 1, 8-10, 33, and 38 of instant application.

Applicant's arguments

Applicant argues that Feijen discloses a process for covalently bonding heparin to a water-soluble protein through an amide linkage. A medical device may then be coated with this protein conjugate by adsorption, but not by covalent binding (Column 3, lines 45-55 of Feijen). Applicant argues that the adsorbed protein may also be cross-linked to itself (protein-protein linkage, Col. 3, lines 56-62 and Col. 4, lines 1-4), but is not covalently bound to the surface of the device. Applicant argues that claim 1, and claims 8- 10, which depend from claim 1, have been amended to specify that the surface to which the modified protein is covalently bound is a metal surface, and Feijen does not disclose a modified protein covalently bound to a metal surface.

Response to Applicant's arguments

It is noted that the amide linkage by an amide bond taught by an amide bond forming agent taught by Feijen et al. is a covalent bond, which is clearly stated in the rejection "covalently bonded conjugates of an anticoagulant and protein that are prepared in the presence of a coupling agent that forms amide linkages between the anticoagulant and the protein (See abstract, Feijen et al., 1987). The limitation "modified protein is covalently bound the metal

surface" recited in claim 1 does not require the amino acid residue of the modified protein directly forms a covalent bond in the absence of a cross linker/coupling agent, whereas the cross linker/coupling agent include SPDP disclosed by the specification and the amide bond forming/coupling agent taught by Feijen et al.

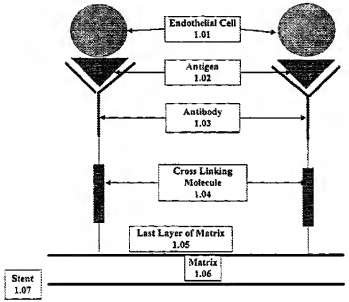
5. Claims 1 and 8-10 remain rejected and newly added claims 33 and 38 are rejected under 35 U.S.C. 102(e) as being anticipated by Kutryk et al. (U.S. patent No. 7,037,332, issued May 2, 2006, filed on 03/15/2001). Applicant's arguments filed 08/20/2008 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 7-8 of the office action mailed on 05/22/2008.

For clarity and completeness of this office action, the rejection for the reasons of record advanced on page 7-8 of the office action mailed on 05/22/2008, is revised below to address claim amendments filed on 08/20/2008.

Claim 1 is drawn to a composition comprising a metal surface and a modified protein covalently bound to the metal surface. Claim 8 further limits the metal surface being a surface of a medical device. Claim 9 further limits claim 8 to medical device selected from the group consisting of a stent, a heart valve, a wire suture, a joint replacement, a urinary dilator, an orthopedic dilator, a catheter and an endotracheal tube. Claim 10 further limits claim 8 to the medical device being at least one of an internal device and an external device. Newly added Claim 33 limits the modified protein comprises at least one of fusion protein and a polypeptide. Claim 38 limits the medical device is coated with a layer of linker and a layer of the modified protein.

Kutryk et al. teaches a composition comprising a medical device coated with one or more antibodies and one or more layers of a matrix, and the matrix may be noncovalently or covalently attached to the medical device, and antibodies may be covalently attached to the matrix using hetero- or homobifunctional cross-linking reagents (See abstract, lines 1-4, column 5, lines 15-55, column 12, and Figure 1, Kutryk et al.).

Figure 1



Kutryk et al. teaches "medical device" refers to a device that is introduced temporarily or permanently into a mammal for the prophylaxis or therapy of a medical condition. These devices include any that are introduced subcutaneously, percutaneously or surgically to rest within an organ, tissue or lumen (which is encompassed by the limitation an internal device recited in claim 10). Medical devices may include, stents, synthetic grafts, artificial heart valves, permanent drug infusion catheters, embolic coils, embolic materials used in vascular embolization (e.g., PVA foams), and vascular sutures. (See lines 50-62, column 5, Kutryk et

al.). Kutryk et al. also teaches using the medical device for endothelial cell binding assay, which is encompassed by the limitation an external device recited in claim 10 of instant application). Kutryk et al. further teaches that stents are composed of metallic structural elements onto which the matrix is applied (See lines 22-24, column 8, Kutryk et al.). It is noted that the broadest and reasonable interpretation of "modified protein" recited in claim 1 and "fusion protein" recited in claim 33, reads on the antibody crossed-linked onto the metal surface of medical device such as a stent taught by Kutryk et al.

Thus, Kutryk et al. clearly anticipate claims 1, 8-10, 33, and 38 of instant application.

Applicant's arguments

Applicant argues that Kutryk discloses a medical device coated with monoclonal or polyclonal antibodies or antibody fragments. Applicant argues that Kutryk does not disclose a composition comprising a metal surface and a modified protein, wherein the modified protein is bound to the metal surface, because the antibodies used by Kutryk are not modified proteins.

Response to Applicant's arguments

It is noted that the limitation "modified protein is covalently bound the metal surface" recited in claim 1 does not require the amino acid residue of the modified protein directly forms a covalent bond in the absence of a cross linker/coupling agent. Kutryk et al. teaches a composition comprising a medical device coated with one or more antibodies and one or more layers of a matrix, and the matrix may be non-covalently or covalently attached to the medical device, and antibodies may be covalently attached to the matrix using hetero- or

homobifunctional cross-linking reagents (See abstract, lines 1-4, column 5, lines 15-55, column 12, and Figure 1, Kutryk et al.).

Claim Rejection - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1, 3, and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Kutryk et al.** (U.S. patent No. 7,037,332, issued May 2, 2006, filed on 03/15/2001) in view of **Xu et al.** (US patent 7,001,745, issued date 02/21/2006, filed on 09/30/1999). *This rejection is necessitated by claim amendment filed by Applicant on 08/20/2208 adding claim 34.*

Kutryk et al. teaches a composition comprising a metal medical device (for instance, a stent) coated with one or more antibodies and one or more layers of a matrix, and the matrix may be covalently attached to the medical device, and antibodies may be covalently attached to the matrix using hetero- or homobifunctional cross-linking reagents (See abstract, lines 1-4, column 5, lines 15-55, column 12, and Figure 1, Kutryk et al.).

Kutryk et al. does not teach "wherein the fusion protein is generated through intein-mediated protein ligation' recited in claim 34.

Xu et al. teaches intein mediated peptide ligation to generate a fusion protein of interest and a method for producing a semi-synthetic fusion protein in vitro, comprising the steps of

producing a target protein fused to a protein splicing element (an intein) and selectively cleaving the fusion and ligating a synthetic protein or peptide at the C-terminal thioester of the target protein (See title and summary of invention, column 1, Xu et al.)

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of Kutryk et al. regarding a composition comprising a metal medical device coated with one or more antibodies and one or more layers of a matrix, and the matrix may be covalently attached to the medical device, and antibodies may be covalently attached to the matrix using hetero- or homobifunctional cross-linking reagents, with the teaching of Xu et al. regarding generation of fusion protein of interest through intein-mediated protein ligation, to arrive at the claimed invention of claims 1, 3 and 34.

One having ordinary skill in the art would have been motivated to combine the teachings of Kutryk et al. and Xu et al. because the intein-mediated protein ligation taught by Xu et al. provide a high-yield, semi-synthetic technique to allow in vitro fusion of a synthetic protein or peptide fragment to an expressed protein without limitation as to the size of the fused fragments.

There would have been a reasonable expectation of success given (i) successful demonstration of a metal medical device coated with one or more antibodies and one or more layers of a matrix, and the matrix being covalently attached to the medical device, and antibodies being covalently attached to the matrix using a cross-linking reagents by the teachings of Kutryk et al., and (ii) successful demonstration of direct ligation of a peptide to the thiester formed between VMA intein and maltose binding protein, by the teachings of Xu et al. (See Figure 3, lines 48-50, column 2, Xu et al.)

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

7. Claims 1, 33, and 35-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Kutryk et al.** (U.S. patent No. 7,037,332, issued May 2, 2006, filed on 03/15/2001) in view of **Xu et al.** (US patent 7,001,745, issued date 02/21/2006, filed on 09/30/1999). *This rejection is necessitated by claim amendment filed by Applicant on 08/20/2208 adding claim 33 and 35-37.*

Kutryk et al. teaches a composition comprising a metal medical device (for instance, a stent) coated with one or more antibodies and one or more layers of a matrix, and the matrix may be covalently attached to the medical device, and antibodies may be covalently attached to the matrix using hetero- or homobifunctional cross-linking reagents (See abstract, lines 1-4, column 5, lines 15-55, column 12, and Figure 1, Kutryk et al.).

Kutryk et al. does not teach "wherein the fusion protein comprises at least a fragment of a CAR protein and a receptor targeting ligand" recited in claim 35, the fragment of the CAR protein recited in claim 36, and the receptor targeting ligand recited in claim 37.

Li teaches the fusion protein comprises extracellular domain of CAR/Hinge/protein A ligand, and Li develops a strategy using adenovirus as an example to demonstrate the strategy of using the fusion protein to re-direct viral tropism (See abstract and Figure 1, Li). Li teaches that any extracellular domain of a viral receptor that is a membrane protein or membrane peptide can be used to replace extracellular domain of CAR and can be inserted as a part of the fusion protein ligand for targeting (See lines 20-24, column 8, Li). Li teaches Arg-Gly-Asp (RGD) motif of viral pentose protein binds to integrins of cell membrane and this binding activates virus internalization via receptor-mediated endocytosis (lines 53-58, column 1, Li)

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of Kutryk et al. regarding a composition comprising a metal medical device coated with one or more antibodies and one or more layers of a matrix, and the matrix may be covalently attached to the medical device, and antibodies may be covalently attached to the matrix using hetero- or homobifunctional cross-linking reagents, with the teaching of Li et al. regarding fusion protein comprises extracellular domain of CAR/receptor targeting ligand, to arrive at the claimed invention of claims 1, 33, and 35-37.

One having ordinary skill in the art would have been motivated to combine the teachings of Kutryk et al. and Li et al. because the fusion protein taught by Li can target specifically the receptor of interest present on cell membrane in the context of using viral vector to deliver therapeutic agent via the metal surface of a medical device, for instance a stent taught by Kutryk et al.

There would have been a reasonable expectation of success given (i) successful demonstration of a metal medical device coated with one or more antibodies and one or more layers of a matrix, and the matrix being covalently attached to the medical device, and antibodies being covalently attached to the matrix using a cross-linking reagents by the teachings of Kutryk et al., and (ii) successful construction of the fusion protein comprises extracellular domain of CAR/receptor targeting ligand, by the teachings of Li.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Conclusion

8. No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, Jr. can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Wu-Cheng Winston Shen/
Patent Examiner
Art Unit 1632

/Thaian N. Ton/
Primary Examiner, Art Unit 1632